NON-YELLOWING AGENT CONTAINING TIZANIDINE HYDROCHLORIDE

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Abstract of **JP7223952**

PURPOSE:To obtain a central acting muscle relaxant containing tizanidine hydrochloride and a non-yellowing excipient and having suppressed yellowing tendency of tizanidine hydrochloride.
CONSTITUTION:This non-yellowing agent contains tizanidine hydrochloride and excipients such as a non-yellowing binder (e.g. polysaccharide such as pullulan), a disintegrant, lactose, corn starch, crystalline cellulose and mannitol. The weight ratio of tizanidine to the excipient is 0.01-10%, preferably 0.2-1%. The agent is used in the form of tablet, capsule, dry syrup, granule, powder, injection, etc., and administered at a daily dose of 3-9mg. Tizanidine hydrochloride is useful as a skeletal muscle relaxant, especially a central acting muscle relaxant having alpha-rigidity and gamma-rigidity suppressing action, multisynaptic reflex suppressing action, anti-impingement action, etc., and effective for the treatment of muscle contraction pain and cerebral and spinal spasmic diseases.

[JP,07-223952,A]

CLAIMS

[Claim(s)]
[Claim 1] tizanidine hydrochloride and yellowing -- a tightness excipient is contained --- less -- yellowing -- a genital center nature muscle relaxant.
[Claim 2] yellowing -- a tightness binder is contained -- being according to claim 1 ---less -- yellowing -- a genital center nature muscle relaxant.
[Claim 3] yellowing -- the central muscle relaxant according to claim 2 whose tightness binder is polysaccharide.
[Claim 4] The central muscle relaxant according to claim 3 whose polysaccharide is a pullulan.
[Claim 5] The central muscle relaxant according to claim 3 whose polysaccharide is gum arabic.
[Claim 6] tizanidine hydrochloride -- yellowing -- the approach of preventing yellowing of the drugs containing the tizanidine hydrochloride which consists of blending a tightness excipient.
[Claim 7] tizanidine hydrochloride -- yellowing -- the approach according to claim 6 of consisting of blending a tightness binder.
[Claim 8] yellowing -- the approach according to claim 7 a tightness binder is polysaccharide.
[Claim 9] The approach according to claim 8 polysaccharide is a pullulan.
[Claim 10] The approach according to claim 8 polysaccharide is gum arabic.
[Claim 11] the object for tizanidine hydrochloride -- yellowing -- a tightness excipient.
[Claim 12] the object for tizanidine hydrochloride -- yellowing -- a tightness binder.

[Translation done.]

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Industrial Application] This invention relates to the drugs which have central muscular relaxation activity. Especially this invention relates to the central muscle relaxant which makes tizanidine hydrochloride an active ingredient.
[0002]
[Description of the Prior Art] It is the matter which has the outstanding activity which is well-known as a skeletal muscle relaxant as a central muscle relaxant which has alpha-rigidity and gamma-rigidity depressant action, polysynaptic reflex depressant action, an anti-infringement operation, etc. as for especially tizanidine hydrochloride, and is used for the therapy of a paramyotonia nature pain, and a cerebral and a spine nature spasm nature disease (clinical evaluation, 14 (1)). 43 (1986), medical Ayumi, 136 (4), 311 (1986), clinician medicine, 1 (4), 533 (1985).
[0003] If in charge of pharmaceutical preparation generally, the approach of blending the excipient which consists of the active ingredient which consists of tizanidine hydrochloride, a binder and lubricant, disintegrator, etc. is taken. However, the problem that yellowing arose by the passage of time after pharmaceutical preparation in this pharmaceutical preparation process for the property of tizanidine hydrochloride had arisen. Moreover, generally, although the binder was used for improving improvement in pharmaceutical preparation nature, and the brittleness of ** in pharmaceutical preparation etc., the binder which does not make tizanidine hydrochloride yellow was not known until now.
[0004] In order to solve this problem, as a result of examining widely the drugs which consist of tizanidine hydrochloride and various excipients, by combining with a specific excipient, this invention person etc. discovers that yellowing of tizanidine hydrochloride is prevented, and completes this invention.
[0005]
[Means for Solving the Problem] namely, this invention -- tizanidine hydrochloride and yellowing -- a tightness excipient is contained ---less -- yellowing -- a genital center nature muscle relaxant is offered.
[0006] this invention -- again -- tizanidine hydrochloride -- yellowing -- the approach of preventing yellowing of the drugs containing the tizanidine hydrochloride which consists of blending a tightness excipient is offered.
[0007] this invention -- further -- the object for tizanidine hydrochloride -- yellowing -- a tightness excipient is offered.
[0008] A binder, disintegrator, etc. are contained in the excipient in this invention. especially -- this invention ---less -- yellowing -- a genital center nature muscle relaxant -- yellowing -- it is desirable to contain a tightness binder. yellowing -- polysaccharide, for example, gum arabic, a pullulan, etc. are contained in a tightness binder.
[0009] Gum arabic is the macromolecule of the molecular weight 240,000-580,000 which uses arabinose, a galactose, rhamnose, guluronic acid, etc. as a principal component, and the thing of the spherical lump of colorlessness thru/or light yellow is said.
[0010] A "pullulan" (excipient specification, Pharmaceutical Affairs Bureau editorial

supervision) is a natural neutral poly saccharide produced from starch by culture of black yeast etc., and a maltotriose carries out a polymerization repeatedly by alpha-1 and 6 chain, and they is tasteless and odorless amorphous amorphous white powder. Hayashibara Biochemical Laboratories, Inc. -- available -- as grade -- PF-20 (a food grade pullulan --) Molecular weight 200,000 description : Amorphous one, amorphous white powder, less than [moisture:6%], pH: 5.0-7.0 (10% water solution), screen analysis : Ten meshes are penetrated. Among 100-150cst. (10wt%, 30 degrees C), and a style-of-pacing:polyethylene bag / carton, Viscosity : 10kg, And PI-20 (demineralization grade of PF-20) property : Tasteless, no odor white powder, Ten etc.kg etc. is in water among a style-of-pacing:polyethylene bag / carton at soluble, ethanol, and the ether refractory, viscosity:100-180cst. (10wt%, 30 degrees C), less than [desiccation deficit:6.0%] (the bottom of 1g and reduced pressure, 90 degrees C, 6 hours), and combustion residue:1.5% (2g).

[0011] As disintegrator, there are H-CMC, CMC and calcium, AcDiSol, L-HPC, an alginic acid, etc.

[0012] As other excipients, they are a lactose, corn starch, crystalline cellulose, a mannitol, PEG6000, and OIDORAGIDDO. - They are L and OIDORAGIDDO. - There are E, EDTA2Na, beta-cyclodextrin (beta-CD), etc.

[0013] "-- yellowing -- the chromaticity difference (deltab) in the color difference measurement described as tightness" below says three or less thing. this -- "-- yellowing -- there are a pullulan and gum arabic as an example of suitable representation of tightness excipient."

[0014] the tizanidine hydrochloride of this invention, and yellowing -- a tightness excipient is contained ---less -- yellowing -- the active ingredient which a genital center nature muscle relaxant becomes from tizanidine hydrochloride -- yellowing -- it can obtain by blending a tightness excipient.

[0015] Although teaser NIJIN and an excipient reach comparatively and this contractor can choose a weight ratio suitably according to the gestalt of pharmaceutical preparation, it is usually 0.01% - 10% of range, and preferably, it is 0.05% - 5% of range, and is 0.1% - 2% of range still more preferably. It is the most desirable in it being 0.2% - 1% of range.

[0016] As formulation, a tablet, a capsule, dry-syrups, a granule, powders, the pharmaceutical preparation for injection, etc. can illustrate.

[0017] As the pharmaceutical preparation approach, the common pharmaceutical preparation approach in this industry of each formulation can apply.

[0018] As a medication method, although internal use, injection, etc. can illustrate, internal use is desirable.

[0019] As a dose, it is an amount comparable as the conventional tizanidine hydrochloride pharmaceutical preparation, and although suitably determined by the age for application, weight, condition of disease, ******, etc., teaser NIJIN is usually about 3mg/day - about 9mg/day as an active ingredient. Usually, a medicine is prescribed for the patient several times per day.

[0020]

[Example] This invention is explained in more detail using an example.

[0021] Example of reference The change-upon-mixing tizanidine hydrochloride, the various excipients, and lactose under severe conditions were ****(ed) as follows, and it

often mixed in the mortar. However, only EDTA2 Na set the addition to 0.02g.
[0022]

Dividing the prepared sample into four equally, one of them remained as it was, it added water, ethanol, and about 1g of 2-propanol to each three which remains, respectively, and performed color difference measurement before and after 60-degree-C 0.5-hour heating, respectively. The Lab method performed color difference measurement using Nippon Denshoku Z-sigma 80 color difference meter. It is thought that this condition is conditions severer than the fluid bed granulation dried while carrying out the spray of the binder solution by adding, being on a water bath and heating a direct solvent to a sample. Moreover, the excipient with which extrude by kneading in a mortar, it is thought that the same actuation as a granulation is added, and a change upon mixing is not accepted to be on this condition can expect not to cause a change upon mixing in an extrusion granulation. A result is shown in Table 1. Front Naka and L are lightness, a and b are chromaticities (hue saturation) and deltab is a yellow chromaticity difference. although the color difference with various excipients showed the difference with the end of mixing to front Naka as a result of color difference measurement -- the blank of only tizanidine hydrochloride and a lactose -- even when -- since change was accepted to some extent in b value by solvent addition, the notation of a visual change showed the result compared with the blank.
[0023]
[Table 1]

[0024]
[Table 2]

[0025] Example 1 The various pharmaceutical preparation (1) tablet following components and daily dose containing a pullulan were corned by wet granulation, and

7.0mmphi flat tip lock was manufactured for 1mg of stearin acid after addition mixing using the tableting machine.
[0026]
[Table 3]

[0027] (2) The capsule following component and the daily dose were corned by wet granulation, and the No. 4 capsule was filled up with 1mg of stearin acid after addition mixing using the encapsulation machine.
[0028]
[Table 4]

[0029] (3) The dry-syrups following component and the daily dose were corned by wet granulation, and dry-syrups were manufactured.
[0030]
[Table 5]

[0031] (4) After mixing the granule following component and a daily dose to homogeneity, it corned by the fluid bed corning method, and the granule was manufactured.
[0032]
[Table 6]

[0033] (5) Fine grain agent (powder)
After mixing the following component and a daily dose to homogeneity, it corned by the agitation granulation method and the fine grain agent was manufactured.
[0034]
[Table 7]

[0035] Example 2 Tablets TA1 (1mg content of gummi arabicum pulveratums) and TA2 (5mg content of gummi arabicum pulveratums) were manufactured like (1) of an example 1 except having used 1mg of gummi arabicum pulveratums, and 5mg instead of the various pharmaceutical preparation (1) tablet pullulans containing gummi arabicum pulveratum.
[0036] (2) Capsules CA1 (1mg content of gummi arabicum pulveratums) and CA2 (5mg content of gummi arabicum pulveratums) were manufactured like (2) of an example 1 except having used 1mg of gummi arabicum pulveratums, and 5mg instead of the capsule pullulan.
[0037] (3) Dry-syrups DA1 (10mg content of gummi arabicum pulveratums) and DA2 (50mg content of gummi arabicum pulveratums) were manufactured like (3) of an example 1 except having used 10mg of gummi arabicum pulveratums, and 50mg for dry-syrups tizanidine hydrochloride instead of 1.144mg and a pullulan.
[0038] (4) Granules GA1 (10mg content of gummi arabicum pulveratums) and GA2 (50mg content of gummi arabicum pulveratums) were manufactured like (4) of an example 1 except having used 10mg of gummi arabicum pulveratums, and 50mg instead of the granule pullulan.
[0039] (5) Fine grain agent (powder)
The fine grain agents PA1 (5mg content of gummi arabicum pulveratums) and PA2 (20mg content of gummi arabicum pulveratums) were manufactured like (5) of an

example 1 except having used 5mg of gummi arabicum pulveratums, and 20mg instead of the pullulan.
[0040] Example 1 of a comparison Tablet TH was manufactured like (1) of an example 1 except having used HPMC5mg instead of the various pharmaceutical preparation (1) tablet pullulans containing HPMC.
[0041] (2) The capsule CH was manufactured like (2) of an example 1 except having used HPMC5mg instead of the capsule pullulan.
[0042] (3) Dry-syrups DH were manufactured like (3) of an example 1 except having used HPMC10mg instead of the dry-syrups pullulan.
[0043] (4) Granule GH was manufactured like (4) of an example 1 except having used HPMC50mg instead of the granule pullulan.
[0044] (5) Fine grain agent (powder)
The fine grain agent PH was manufactured like (5) of an example 1 except having used HPMC20mg instead of the pullulan.
[0045] Example 2 of a comparison When the tablet was manufactured and warm air desiccation was carried out at 40 degrees C like (1) of an example 1 except having used HPC5mg instead of the various pharmaceutical preparation (1) tablet pullulans containing HPC, the granulation object yellowed.
[0046] (2) When the capsule was manufactured and warm air desiccation was carried out at 40 degrees C like (2) of an example 1 except having used HPC5mg instead of the capsule pullulan, the granulation object yellowed.
[0047] (3) Except having used HPC10mg instead of the dry-syrups pullulan, like (3) of an example 1, when dry-syrups were manufactured, it left and **** yellowed to ******.
[0048] (4) Except having used HPC50mg instead of the granule pullulan, like (4) of an example 1, when the granule was manufactured, the granulation object yellowed.
[0049] (5) Fine grain agent (powder)
Except having used HPC20mg instead of the pullulan, like (5) of an example 1, when the fine grain agent was manufactured, the granulation object yellowed.
[0050] Example 3 of a comparison When the tablet was manufactured and warm air desiccation was carried out at 40 degrees C like (1) of an example 1 except having used PVP5mg instead of the various pharmaceutical preparation (1) tablet pullulans containing PVP, the granulation object yellowed.
[0051] (2) When the capsule was manufactured and warm air desiccation was carried out at 40 degrees C like (2) of an example 1 except having used PVP5mg instead of the capsule pullulan, the granulation object yellowed.
[0052] (3) Except having used PVP10mg instead of the dry-syrups pullulan, like (3) of an example 1, when dry-syrups were manufactured, it left and **** yellowed to ******.
[0053] (4) Except having used PVP50mg instead of the granule pullulan, like (4) of an example 1, when the granule was manufactured, the granulation object yellowed.
[0054] (5) Fine grain agent (powder)
Except having used PVP20mg instead of the pullulan, like (5) of an example 1, when the fine grain agent was manufactured, the granulation object yellowed.
[0055] It saves for ten days under 4 conditions of 50 degrees C of the drugs manufactured in the stability test examples 1-2 and the example 1 of a comparison, 50-degree-C85%RH, 60 degrees C, and 60-degree-C80%RH, and the result of having observed appearance change of each pharmaceutical preparation is shown in Table 2. However, the

capsule observed change of contents.
[0056]
[Table 8]